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A Study of Aminoglutethemide and Hydrocortisone in Patients with Advanced and Refractory Prostate Carcinoma

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We have studied aminoglutethemide (AG) combined with hydrocortisone in 28 patients with advanced and refractory prostate carcinoma. All the patients had failed at least one endocrine therapy. Six patients received only one prior hormonal treatment. Five patients were off study within 3 weeks due to early death and toxicity, 14 had progressive disease, and 9 had stable disease. No objective partial remission was observed, but the nine stable patients had therapeutic benefit, with improvement in bone pain and performance status for a median duration of 153 days. Three patients withdrew because of postural hypotension, dizziness, weakness, and lethargy. The median survival of the entire group was 186 days (range 41–606 days). Our results suggest that aminoglutethemide and hydrocortisone can be an alternative treatment for patients with advanced and refractory prostate carcinoma.
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Patients with stage D2 metastatic adenocarcinoma of the prostate gland are usually managed with hormonal manipulation to ablate androgen for controlling symptoms (1–3). Androgen ablation can be achieved either by giving patients additive hormones, such as estrogen, progestational agent (4), luteinizing hormone–releasing hormone agonist (LH–RH) (5), or bilateral orchiectomy (6). Although the majority of patients will respond to the initial hormonal therapy, almost all patients will relapse with disease progression within 2–3 years. Then, the disease assumes a more rapid and progressive downhill course. The median survival in this group of patients with hormone-refractory prostate carcinoma is only about 6 months (2,7,8). These patients do not usually respond to secondary hormone treatment, such as megestrol acetate, leuprolide (9,10), or chemotherapy (11). The mechanism of the resistance to therapy remains largely unknown.

The adrenal steroid production is also a source of serum androgen and is not affected by most primary hormonal therapy directed to suppress the testicular androgen (12). Aminoglutethemide inhibits the synthesis of adrenal androgen (13), and hydrocortisone suppresses the compensatory increase of adrenocorticotropin. It is prudent to employ secondary hormonal manipulation with a different mechanism of action from the first one. Hence, we evaluated the palliative effect of the combination of aminoglutethemide and hydrocortisone in 28 patients with advanced and refractory prostate carcinoma.

MATERIALS AND METHODS

Patients with histologically documented prostate carcinoma and metastatic disease (stage D2) that had

become refractory to hormonal management were eligible. Patients with uncontrolled congestive heart failure, cardiac arrhythmia, or hypertension were excluded. Prior chemotherapy was allowed for patient entry.

All patients received aminoglutethemide (Cytadren, supplied by CIBA Co., Summit, NJ, U.S.A.), 250 mg p.o., q.i.d., and hydrocortisone, 20 mg q.i.d., at the same time. After the first week of treatment, the dose of hydrocortisone was reduced to 10 mg q.i.d. in patients with stable disease so as to reduce the potential side effects of hypercorticism. Patients were evaluated once a week for the first 4 weeks, with history, physical examination, and performance status. If the patient's condition was stable after 4 weeks, he was then followed every 4 weeks until disease progression occurred. Complete blood counts, chemistry, and acid phosphatase were done every month and bone scan every 3–6 months. We applied the response criteria of the National Prostate Cooperative Projects (NPCP) to evaluate treatment results (14).

RESULTS

All patients registered on the study were included in the analysis of response and toxicity. Five patients had an inadequate trial of treatment and were viewed as treatment failures (one each with subdural hemorrhage, cardiac arrest, and pneumonia; two patients died within 21 days on study). The characteristics of the patients were shown in Table 1. The median performance status and number of prior therapies were both 2. All the patients had failed hormonal treatment. The toxicity of treatment is shown in Table 2. The side effects of dizziness, lethargy, weakness, and postural hypotension were severe enough that three patients withdrew from the study in spite of the use of mineralocorticoid (Florinef acetate, 0.1–0.3 mg/day). Dizziness, nausea, and vomiting were common, but tolerable, except in one patient who refused further therapy. Skin rash occurred transiently in three patients. Fourteen patients had progressive disease without any response. Nine patients had stable disease and obtained significant improvement of bone pain and performance status for a median duration of 153 days (range 90–380 days). Four of these patients experienced less bone pain and a sense of well-being in the first month of treatment. Three patients showed dramatic improvement of their performance status, which changed from bedridden to ambulatory within the first 2 weeks on study. The mean age of patients with stable disease was 71 (range 63–85), which was the same as that in patients with progressive disease.

TABLE 1. *Patients characteristics*

Age (range)	71 (46–85)
Performance status (no. of patients)	
1	12
2	9
3	4
4	3
Prior therapy (no. of patients)	
Orchiectomy	13 (5)*
Diethylstilbestrol	22 (8)
Chemotherapy	6 (2)
Tamoxifen	3 (0)
Megestrol Acetate	1 (0)
Disease sites (no. of patients)	
Osseous only	24
Visceral only	0
Osseous and visceral	4
No. of prior therapies (no. of patients)	
1	6 (3)*
2	10 (3)
3	7 (1)
4	4 (2)
5	1 (0)

* The number in parentheses denotes patients with improvement of bone pain.

TABLE 2. *Toxicity of aminoglutethemide and hydrocortisone*

	No. of patients (%)
Ataxia	1 (3.6)
Peripheral edema	2 (7.1)
Skin rash	3 (10.7)
Fever	4 (14.3)
Postural hypotension	4 (14.3)
Nausea/vomiting	6 (21.4)
Dizziness, lethargy	8 (28.6)

No objective partial remissions were observed. Two patients had a reduction of serum acid phosphatase of more than 50% from the pretreatment level, and one patient's acid phosphatase returned to the normal range after treatment. The median times to treatment failure and survival for the entire group were 80 and 186 days, respectively, and for the stable patients alone, they were 153 and 331 days, respectively.

DISCUSSION

Most of our patients had disease refractory to multiple treatment modalities. Only six patients had failed from one endocrine treatment. Our results demonstrate the therapeutic benefit of improving bone pain and performance status from aminoglutethemide and hydrocortisone in 9 of 28 (32%) heavily pretreated patients. Two of six patients with prior chemotherapy also had improvement of bone pain. The toxicities were similar to those previously reported. They were not negligible, but were tolerable most of the time by our patients. It is possible that toxicity could be less if we

exclude patients with poor performance status and multiple treatment failures.

Drago et al. (15) have reported that aminoglutethemide had a 16% objective response and 24% stable disease in 43 patients with metastatic prostate carcinoma after initial treatment failure. Ahmann et al. (16) also reported a 13% objective partial remission and 48% stable disease in 86 patients who had failed only from orchiectomy. Thus, both studies employed aminoglutethemide and hydrocortisone as the second hormonal treatment with moderate success. However, Block et al. (17) reported no objective or subjective response in 23 patients, but only 4 of their patients were first-line failures. Our patient population is similar to those in Block's report. The observation of subjective symptomatic relief in our patients is different from their report. The reason for this discrepancy is unknown. Those reports by Lippman et al. (18) and Rostom et al. (19) showed subjective improvement of bone pain in 50% and 75% of patients, respectively, and are consistent with our findings. As only four patients in our study had an objectively measurable disease, we did not expect to observe any objective partial response. Bilateral adrenalectomy has also been reported to produce 20–40% clinical response (20). Hence, we regard adrenal androgen ablation is an alternative treatment for patients with hormone-refractory prostate carcinoma. We believe that the combination of aminoglutethemide and hydrocortisone can be used as second-line hormonal therapy and in place of bilateral adrenalectomy.

It is unclear which is the best second-line hormonal treatment in patients with metastatic prostate carcinoma, although most investigators agree that second endocrine manipulation seldom produces objective remission (21). Considering available agents, aminoglutethemide and hydrocortisone offer the advantage of costing less than leuprolide (9), estramustine phosphate (22), or Ketoconazole (23) and are possibly more beneficial in relieving symptoms than leuprolide (9) or megestrol acetate (10). However, definite conclusion requires future randomized studies that should also include a placebo control arm to accurately assess the therapeutic effect of second-line hormonal treatment.

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